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4-(2-Phenyloxyphenyl)-piperidine or -1,2,3,6-tetrahydropyridine derivatives as serotonin reuptake inhibitors

The present invention relates to novel compounds which are serotonin reuptake inhibitors and as such effective in the treatment of for example depression and anxiety.

Background of the invention

10 Selective serotonin reuptake inhibitors (hereinafter referred to as SSRIs) have become first choice therapeutics in the treatment of depression, certain forms of anxiety and social phobias, because they are effective, well tolerated and have a favourable safety profile compared to the classic tricyclic antidepressants.

15 However, clinical studies on depression indicate that non-response to SSRIs is substantial, up to 30%. Another, often neglected, factor in antidepressant treatment is compliance, which has a rather profound effect on the patient's motivation to continue pharmacotherapy.

20 First of all, there is the delay in therapeutic effect of SSRIs. Sometimes symptoms even worsen during the first weeks of treatment. Secondly, sexual dysfunction is a side effect common to all SSRIs. Without addressing these problems, real progress in the pharmacotherapy of depression and anxiety disorders is not likely to happen.

25 The combined effect of serotonin reuptake inhibition and norepinephrine uptake inhibition on depression is explored in clinical studies of compounds such as Duloxetine (Wong, Duloxetine (LY-248686): an inhibitor of serotonin and noradrenaline uptake and an antidepressant drug candidate *Expert Opinion on Investigational Drugs*, 1998, 7, 10, 1691-1699) and Venlafaxine (Khan-A et al,
30 Venlafaxine in depressed outpatients *Psychopharmacology Bulletin*, 1991, 27, 141-144).

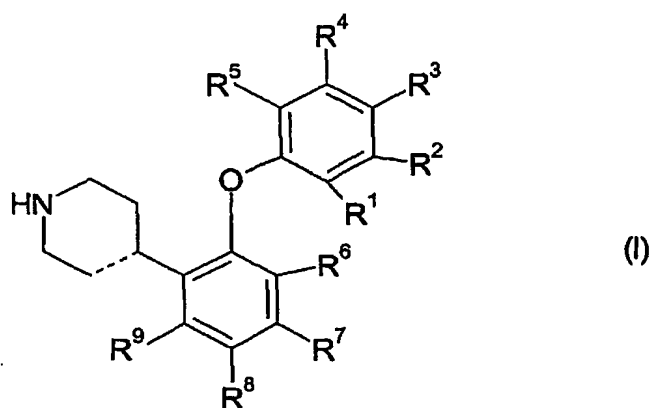
The present invention provides novel compounds which possess the combined effect of serotonin reuptake inhibition and norepinephrine uptake inhibition for the treatment of

affective disorders, such as depression, anxiety disorders including general anxiety disorder, social anxiety disorder, post traumatic stress disorder, obsessive compulsive disorder, panic disorder, panic attacks, specific phobias, social phobia and agoraphobia.

5

Summary of the invention

The present invention provides compounds of the general formula I



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wherein the dotted line, R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, and R⁹ are as defined below.

The invention provides a compound according to the above for use as a medicament.

15 The invention provides a pharmaceutical composition comprising a compound according to the above or a pharmaceutically acceptable acid addition salt thereof and at least one pharmaceutically acceptable carrier or diluent.

The invention provides the use of a compound according to the above or a
20 pharmaceutically acceptable acid addition salt thereof for the preparation of a medicament for the treatment of affective disorders, such as depression, anxiety disorders including general anxiety disorder, social anxiety disorder, post traumatic stress disorder, obsessive compulsive disorder, panic disorder, panic attacks, specific phobias, social phobia and agoraphobia.

25

The invention provides a method for the treatment of an affective disorders, such as depression, anxiety disorders including general anxiety disorder, social anxiety disorder, post traumatic stress disorder, obsessive compulsive disorder, panic disorder, panic attacks, specific phobias, social phobia and angoraphobia in a living animal
 5 body, including a human, comprising administering a therapeutically effective amount of a compound according to the above or a pharmaceutically acceptable acid addition salt thereof.

Definition of substituents

10

Halogen means fluoro, chloro, bromo or iodo.

The expression C₁₋₆-alk(en/yn)yl means a C₁₋₆-alkyl, C₂₋₆-alkenyl or a C₂₋₆-alkynyl group.

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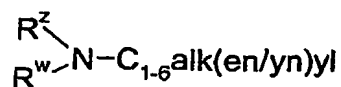
The term C₁₋₆ alkyl refers to a branched or unbranched alkyl group having from one to six carbon atoms inclusive, including but not limited to methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2-methyl-2-propyl and 2-methyl-1-propyl.

20 Similarly, C₂₋₆ alkenyl and C₂₋₆ alkynyl, respectively, designate such groups having from two to six carbon atoms, including one double bond and one triple bond respectively, including but not limited to ethenyl, propenyl, butenyl, ethynyl, propynyl and butynyl.

25 The terms C₁₋₆-alk(en/yn)oxy, C₁₋₆ alk(en/yn)ylsulfanyl, hydroxy-C₁₋₆-alk(en/yn)yl, halo-C₁₋₆-alk(en/yn)yl, cyano-C₁₋₆-alk(en/yn)yl, NR^zR^w-C₁₋₆-alk(en/yn)yl, C₁₋₆-alk(en/yn)oxy-C₁₋₆-alk(en/yn)yl and halo-C₁₋₆-alk(en/yn)oxy designate such groups in which the C₁₋₆-alk(en/yn)yl are as defined above. Halo means halogen.

NR^zR^w-C₁₋₆-alk(en/yn)yl designate the group

30



The term C₃₋₈ cycloalkyl designates a monocyclic or bicyclic carbocycle having three to eight C-atoms, including but not limited to cyclopropyl, cyclopentyl, cyclohexyl, etc.

- 5 The term C₃₋₈ cycloalkenyl designates a monocyclic or bicyclic carbocycle having three to eight C-atoms and including one double bond.

In the term C₃₋₈-cycloalk(en)yl-C₁₋₆-alk(en/yn)yl, C₃₋₈-cycloalk(en)yl and C₁₋₆-alk(en/yn)yl are as defined above.

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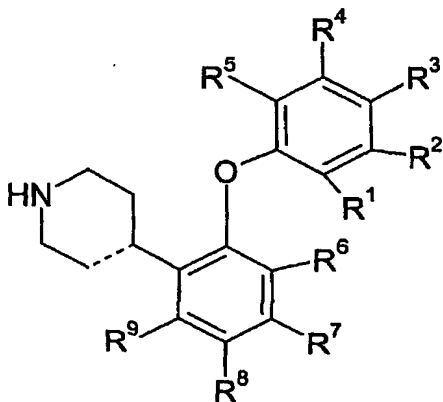
- The term 3-7-membered ring optionally containing one further heteroatom, such as N, O, or S, as used herein refers to ring systems such as 1-morpholinyl, 1-piperidinyl, 1-azepinyl, 1-piperazinyl, 1-homopiperazinyl, 1-imidazolyl, 1-pyrrolidinyl, 1-azetidiny, 1-pyrrolyl or pyrazolyl, all of which may be further substituted with a group selected from a C₁₋₆-alk(en/yn)yl, hydroxy, hydroxy-C₁₋₆-alk(en/yn)yl, C₁₋₆-alk(en/yn)oxy-C₁₋₆-alk(en/yn)yl.

15

Description of the invention

- 20 The present invention relates to 4-(2-phenyloxyphenyl)-piperidine or -1,2,3,6-tetrahydropyridine derivatives which are serotonin reuptake inhibitors and as such effective in the treatment of for example depression and anxiety.

- Accordingly the present invention relates to a compound represented by the general
25 formula I



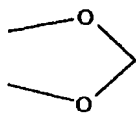
(I)

Wherein

the dotted line ---- indicates a single bond or a double bond;

- 5 R^1, R^2, R^3, R^4, R^5 are independently selected from hydrogen, halogen, cyano, C_{1-6} -alk(en/yn)yl, C_{1-6} -alk(en/yn)yloxy, C_{1-6} -alk(en/yn)ylsulfanyl, hydroxy, hydroxy- C_{1-6} -alk(en/yn)yl, halo- C_{1-6} -alk(en/yn)yl, halo- C_{1-6} -alk(en/yn)yloxy, or NR^xR^y wherein R^x and R^y are independently selected from hydrogen, C_{1-6} -alk(en/yn)yl, cyano- C_{1-6} -alk(en/yn)yl, C_{3-8} -cycloalk(en)yl, C_{3-8} -cycloalk(en)yl- C_{1-6} -alk(en/yn)yl, or NR^zR^w - C_{1-6} -alk(en/yn)yl, wherein R^z and R^w are independently selected from hydrogen, C_{1-6} -alk(en/yn)yl, C_{3-8} -cycloalk(en)yl, or C_{3-8} -cycloalk(en)yl- C_{1-6} -alk(en/yn)yl; or R^x and R^y together with the nitrogen to which they are attached form a 3-7-membered ring which optionally contains one further heteroatom; or

- 15 R^2 and R^3 together form a heterocycle fused to the phenyl ring selected from



; and R^1, R^4, R^5 are as defined above;

- R^6, R^7, R^8, R^9 are independently selected from hydrogen, halogen, C_{1-6} -alk(en/yn)yl, C_{1-6} -alk(en/yn)yloxy, C_{1-6} -alk(en/yn)ylsulfanyl, hydroxy, hydroxy- C_{1-6} -alk(en/yn)yl, halo- C_{1-6} -alk(en/yn)yl, halo- C_{1-6} -alk(en/yn)yloxy, or NR^xR^y wherein R^x and R^y are independently selected from hydrogen, C_{1-6} -alk(en/yn)yl, cyano- C_{1-6} -alk(en/yn)yl, C_{3-8} -cycloalk(en)yl, C_{3-8} -cycloalk(en)yl- C_{1-6} -alk(en/yn)yl, or NR^zR^w - C_{1-6} -alk(en/yn)yl, wherein R^z and R^w are independently selected from hydrogen, C_{1-6} -alk(en/yn)yl, C_{3-8} -cycloalk(en)yl, or C_{3-8} -cycloalk(en)yl- C_{1-6} -alk(en/yn)yl; or R^x and R^y together with the nitrogen to which they are attached form a 3-7-membered ring which optionally contains one further heteroatom;

provided that at least one of $R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8$, and R^9 is different from hydrogen;

- 30 or a salt thereof.

In one embodiment of the compound of formula I R^1 is selected from hydrogen, halogen, cyano, C_{1-6} -alk(en/yn)yl, C_{1-6} -alk(en/yn)oxy, C_{1-6} -alk(en/yn)ylsulfanyl, halo- C_{1-6} -alk(en/yn)yl, or NR^xR^y wherein R^x and R^y are independently selected from hydrogen, C_{1-6} -alk(en/yn)yl, cyano- C_{1-6} -alk(en/yn)yl, C_{3-8} -cycloalk(en)yl, C_{3-8} -cycloalk(en)yl- C_{1-6} -alk(en/yn)yl, or NR^zR^w - C_{1-6} -alk(en/yn)yl, wherein R^z and R^w are independently selected from hydrogen, C_{1-6} -alk(en/yn)yl, C_{3-8} -cycloalk(en)yl, or C_{3-8} -cycloalk(en)yl- C_{1-6} -alk(en/yn)yl, provided that if one of R^x and R^y is NR^zR^w - C_{1-6} -alk(en/yn)yl then the other is selected from hydrogen, C_{1-6} -alk(en/yn)yl, cyano- C_{1-6} -alk(en/yn)yl, C_{3-8} -cycloalk(en)yl, or C_{3-8} -cycloalk(en)yl- C_{1-6} -alk(en/yn)yl; or R^x and R^y together with the nitrogen to which they are attached form a 3-7-membered ring which optionally contains one further heteroatom. In a further embodiment of the compound of formula I R^1 is selected from hydrogen, halogen, cyano, C_{1-6} -alk(en/yn)yl, C_{1-6} -alk(en/yn)oxy, C_{1-6} -alk(en/yn)ylsulfanyl, halo- C_{1-6} -alk(en/yn)yl. In a further embodiment R^1 is NR^xR^y wherein R^x and R^y are independently selected from hydrogen, C_{1-6} -alk(en/yn)yl, cyano- C_{1-6} -alk(en/yn)yl, C_{3-8} -cycloalk(en)yl, C_{3-8} -cycloalk(en)yl- C_{1-6} -alk(en/yn)yl, such as hydrogen, cyanomethyl, C_{1-6} -alk(en/yn)yl. In a further embodiment R^1 is NR^xR^y wherein R^x is NR^zR^w - C_{1-6} -alk(en/yn)yl, wherein R^z and R^w are independently selected from hydrogen, C_{1-6} -alk(en/yn)yl, C_{3-8} -cycloalk(en)yl, or C_{3-8} -cycloalk(en)yl- C_{1-6} -alk(en/yn)yl, and R^y is selected from hydrogen, C_{1-6} -alk(en/yn)yl, cyano- C_{1-6} -alk(en/yn)yl, C_{3-8} -cycloalk(en)yl, or C_{3-8} -cycloalk(en)yl- C_{1-6} -alk(en/yn)yl. In a further embodiment R^1 is NR^xR^y wherein R^x and R^y together with the nitrogen to which they are attached form a 3-7-membered ring which optionally contains one further heteroatom, such as 1-morpholinyl, 1-piperidinyl, 1-azepinyl, 1-piperazinyl, 1-homopiperazinyl, 1-imidazolyl, 1-pyrrolidinyl, 1-azetidyl, 1-pyrrolyl or pyrazolyl, optionally substituted with one or more selected from a C_{1-6} -alk(en/yn)yl, hydroxy, hydroxy- C_{1-6} -alk(en/yn)yl, C_{1-6} -alk(en/yn)oxy- C_{1-6} -alk(en/yn)yl, e.g. one or two selected from hydroxy, hydroxy- C_{1-6} -alkyl, C_{1-6} -alkyloxy- C_{1-6} -alkyl, C_{1-6} -alkyl, in particular one or two selected from hydroxy, methoxy-methyl, methyl. Typically, R^1 is selected from hydrogen; halogen; cyano; C_{1-6} -alkyl; C_{1-6} -alkyloxy; C_{1-6} -alkylsulfanyl; halo- C_{1-6} -alkyl; NR^xR^y wherein R^x and R^y are independently selected from hydrogen, C_{1-6} -alkyl, cyanomethyl; NR^xR^y wherein R^y is selected from hydrogen, or C_{1-6} -alkyl, and R^x is NR^zR^w - C_{1-6} -alk(en/yn)yl wherein R^z and R^w are independently selected from hydrogen, or C_{1-6} -

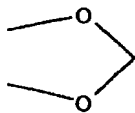
alkyl; 1-morpholinyl, 1-piperidinyl, 1-azepinyl, 1-piperazinyl, 1-homopiperazinyl, 1-imidazolyl, 1-pyrrolidinyl, 1-azetidiny, 1-pyrrolyl or pyrazolyl, optionally substituted with one or two selected from hydroxy, hydroxy-C₁₋₆-alkyl, C₁₋₆-alkyloxy-C₁₋₆-alkyl, C₁₋₆-alkyl, in particular one or two selected from hydroxy, methoxy-methyl, methyl.

- 5 To further illustrate without limiting the invention an embodiment of R¹ is hydrogen; another embodiment of R¹ is C₁₋₆-alkyl, such as methyl; a further embodiment of R¹ is halogen, such as fluoro, or chloro.

- 10 In a further embodiment of the compound of formula I R² is selected from hydrogen, halogen, cyano, C₁₋₆-alk(en/yn)yl, C₁₋₆-alk(en/yn)yl, C₁₋₆-alk(en/yn)ylsulfanyl, halo-C₁₋₆-alk(en/yn)yl. Typically, R² is selected from hydrogen, halogen, cyano, C₁₋₆-alkyl, C₁₋₆-alkyloxy, C₁₋₆-alkylsulfanyl, halo-C₁₋₆-alkyl. To further illustrate without limiting the invention an embodiment of R² is hydrogen; another embodiment of R² is C₁₋₆-alkoxy, such as methoxy.

- 15 In a further embodiment of the compound of formula I R³ is selected from hydrogen, halogen, cyano, C₁₋₆-alk(en/yn)yl, C₁₋₆-alk(en/yn)yl, C₁₋₆-alk(en/yn)ylsulfanyl, halo-C₁₋₆-alk(en/yn)yl. Typically, R³ is selected from hydrogen, halogen, cyano, C₁₋₆-alkyl, C₁₋₆-alkyloxy, C₁₋₆-alkylsulfanyl, halo-C₁₋₆-alkyl. To further illustrate without limiting the invention an embodiment of R³ is hydrogen; another embodiment of R³ is C₁₋₆-alkyl, such as methyl; a further embodiment of R³ is C₁₋₆-alkoxy, such as methoxy; a further embodiment of R³ is halogen, such as chloro, or fluoro.

- 25 In a further embodiment of the compound of formula I R² and R³ together form a heterocycle fused to the phenyl ring selected from



- 30 In a further embodiment of the compound of formula I R⁴ is selected from hydrogen, halogen, cyano, C₁₋₆-alk(en/yn)yl, C₁₋₆-alk(en/yn)yl, C₁₋₆-alk(en/yn)ylsulfanyl, halo-C₁₋₆-alk(en/yn)yl. Typically, R⁴ is selected from hydrogen, halogen, cyano, C₁₋₆-alkyl, C₁₋₆-alkyloxy, C₁₋₆-alkylsulfanyl, halo-C₁₋₆-alkyl. To further illustrate without

limiting the invention an embodiment of R^4 is hydrogen; another embodiment of R^4 is C_{1-6} -alkoxy, such as methoxy.

In a further embodiment of the compound of formula I R^5 is selected from hydrogen,
5 halogen, cyano, C_{1-6} -alk(en/yn)yl, C_{1-6} -alk(en/yn)yl, C_{1-6} -alk(en/yn)ylsulfanyl,
halo- C_{1-6} -alk(en/yn)yl, or NR^xR^y wherein R^x and R^y are independently selected from
hydrogen, C_{1-6} -alk(en/yn)yl, cyano- C_{1-6} -alk(en/yn)yl, C_{3-8} -cycloalk(en)yl, C_{3-8} -
cycloalk(en)yl- C_{1-6} -alk(en/yn)yl, or NR^zR^w - C_{1-6} -alk(en/yn)yl, wherein R^z and R^w are
10 independently selected from hydrogen, C_{1-6} -alk(en/yn)yl, C_{3-8} -cycloalk(en)yl, or C_{3-8} -
cycloalk(en)yl- C_{1-6} -alk(en/yn)yl, provided that if one of R^x and R^y is NR^zR^w - C_{1-6} -
alk(en/yn)yl then the other is selected from hydrogen, C_{1-6} -alk(en/yn)yl, cyano- C_{1-6} -
alk(en/yn)yl, C_{3-8} -cycloalk(en)yl; or C_{3-8} -cycloalk(en)yl- C_{1-6} -alk(en/yn)yl; or R^x and
 R^y together with the nitrogen to which they are attached form a 3-7-membered ring
which optionally contains one further heteroatom. In a further embodiment of the
15 compound of formula I R^5 is selected from hydrogen, halogen, cyano, C_{1-6} -
alk(en/yn)yl, C_{1-6} -alk(en/yn)yl, C_{1-6} -alk(en/yn)ylsulfanyl, halo- C_{1-6} -alk(en/yn)yl.
In a further embodiment R^5 is NR^xR^y wherein R^x and R^y are independently selected
from hydrogen, C_{1-6} -alk(en/yn)yl, cyano- C_{1-6} -alk(en/yn)yl, C_{3-8} -cycloalk(en)yl, C_{3-8} -
cycloalk(en)yl- C_{1-6} -alk(en/yn)yl, such as hydrogen, cyanomethyl, C_{1-6} -alk(en/yn)yl. In
20 a further embodiment R^5 is NR^xR^y wherein R^x is NR^zR^w - C_{1-6} -alk(en/yn)yl, wherein R^z
and R^w are independently selected from hydrogen, C_{1-6} -alk(en/yn)yl, C_{3-8} -
cycloalk(en)yl, or C_{3-8} -cycloalk(en)yl- C_{1-6} -alk(en/yn)yl, and R^y is selected from
hydrogen, C_{1-6} -alk(en/yn)yl, cyano- C_{1-6} -alk(en/yn)yl, C_{3-8} -cycloalk(en)yl, or C_{3-8} -
cycloalk(en)yl- C_{1-6} -alk(en/yn)yl. In a further embodiment R^5 is NR^xR^y wherein R^x
25 and R^y together with the nitrogen to which they are attached form a 3-7-membered
ring which optionally contains one further heteroatom, such as 1-morpholinyl, 1-
piperidinyl, 1-azepinyl, 1-piperazinyl, 1-homopiperazinyl, 1-imidazolyl, 1-
pyrrolidinyl, 1-azetidyl, 1-pyrrolyl or pyrazolyl, optionally substituted with one or
more selected from a C_{1-6} -alk(en/yn)yl, hydroxy, hydroxy- C_{1-6} -alk(en/yn)yl, C_{1-6} -
30 alk(en/yn)yl, C_{1-6} -alk(en/yn)yl, e.g. one or two selected from hydroxy, hydroxy- C_{1-6} -
alkyl, C_{1-6} -alkoxy- C_{1-6} -alkyl, C_{1-6} -alkyl, in particular one or two selected from
hydroxy, methoxy-methyl, methyl. Typically, R^5 is selected from hydrogen; halogen;
cyano; C_{1-6} -alkyl; C_{1-6} -alkoxy; C_{1-6} -alkylsulfanyl; halo- C_{1-6} -alkyl; NR^xR^y wherein

R^x and R^y are independently selected from hydrogen, C_{1-6} -alkyl, cyanomethyl; NR^xR^y wherein R^y is selected from hydrogen, or C_{1-6} -alkyl, and R^x is NR^zR^w - C_{1-6} -alk(en/yn)yl wherein R^z and R^w are independently selected from hydrogen, or C_{1-6} -alkyl; 1-morpholinyl, 1-piperidinyl, 1-azepinyl, 1-piperazinyl, 1-homopiperazinyl, 1-imidazolyl, 1-pyrrolidinyl, 1-azetidyl, 1-pyrrolyl or pyrazolyl, optionally substituted with one or two selected from hydroxy, hydroxy- C_{1-6} -alkyl, C_{1-6} -alkyloxy- C_{1-6} -alkyl, C_{1-6} -alkyl, in particular one or two selected from hydroxy, methoxy-methyl, methyl. To further illustrate without limiting the invention an embodiment of R^5 is hydrogen; another embodiment of R^5 is C_{1-6} -alkyl, such as methyl; a further embodiment of R^5 is halogen, such as chloro, or fluoro.

In a further embodiment of the compound of formula I R^6 is selected from hydrogen, halogen, C_{1-6} -alk(en/yn)yl, halo- C_{1-6} -alk(en/yn)yl. Typically, R^6 is selected from hydrogen, halogen, C_{1-6} -alkyl, halo- C_{1-6} -alkyl. To further illustrate without limiting the invention an embodiment of R^6 is hydrogen; another embodiment of R^6 is halogen, such as fluoro.

In a further embodiment of the compound of formula I R^7 is selected from hydrogen, halogen, C_{1-6} -alk(en/yn)yl, halo- C_{1-6} -alk(en/yn)yl. Typically, R^7 is selected from hydrogen, halogen, C_{1-6} -alkyl, halo- C_{1-6} -alkyl. To further illustrate without limiting the invention an embodiment of R^7 is hydrogen; another embodiment of R^7 is halogen, such as fluoro.

In a further embodiment of the compound of formula I R^8 is selected from hydrogen, halogen, C_{1-6} -alk(en/yn)yl, halo- C_{1-6} -alk(en/yn)yl, or NR^xR^y wherein R^x and R^y are independently selected from hydrogen, C_{1-6} -alk(en/yn)yl, cyano- C_{1-6} -alk(en/yn)yl, C_{3-8} -cycloalk(en)yl, C_{3-8} -cycloalk(en)yl- C_{1-6} -alk(en/yn)yl, or NR^zR^w - C_{1-6} -alk(en/yn)yl, wherein R^z and R^w are independently selected from hydrogen, C_{1-6} -alk(en/yn)yl, C_{3-8} -cycloalk(en)yl, or C_{3-8} -cycloalk(en)yl- C_{1-6} -alk(en/yn)yl, provided that if one of R^x and R^y is NR^zR^w - C_{1-6} -alk(en/yn)yl then the other is selected from hydrogen, C_{1-6} -alk(en/yn)yl, cyano- C_{1-6} -alk(en/yn)yl, C_{3-8} -cycloalk(en)yl, or C_{3-8} -cycloalk(en)yl- C_{1-6} -alk(en/yn)yl; or R^x and R^y together with the nitrogen to which they are attached form a 3-7-membered ring which optionally contains one further heteroatom. In a further

embodiment of the compound of formula I R^8 is selected from hydrogen, halogen, C_{1-6} -alk(en/yn)yl, halo- C_{1-6} -alk(en/yn)yl. In a further embodiment R^8 is NR^xR^y wherein R^x and R^y are independently selected from hydrogen, C_{1-6} -alk(en/yn)yl, cyano- C_{1-6} -alk(en/yn)yl, C_{3-8} -cycloalk(en)yl, C_{3-8} -cycloalk(en)yl- C_{1-6} -alk(en/yn)yl, such as
5 hydrogen, cyanomethyl, C_{1-6} -alk(en/yn)yl. In a further embodiment R^8 is NR^xR^y wherein R^x is NR^zR^w - C_{1-6} -alk(en/yn)yl, wherein R^z and R^w are independently selected from hydrogen, C_{1-6} -alk(en/yn)yl, C_{3-8} -cycloalk(en)yl, or C_{3-8} -cycloalk(en)yl- C_{1-6} -alk(en/yn)yl, and R^y is selected from hydrogen, C_{1-6} -alk(en/yn)yl, cyano- C_{1-6} -alk(en/yn)yl, C_{3-8} -cycloalk(en)yl, or C_{3-8} -cycloalk(en)yl- C_{1-6} -alk(en/yn)yl. In a further
10 embodiment R^8 is NR^xR^y wherein R^x and R^y together with the nitrogen to which they are attached form a 3-7-membered ring which optionally contains one further heteroatom, such as 1-morpholinyl, 1-piperidinyl, 1-azepinyl, 1-piperazinyl, 1-homopiperazinyl, 1-imidazolyl, 1-pyrrolidinyl, 1-azetidyl, 1-pyrrolyl or pyrazolyl, optionally substituted with one or more selected from a C_{1-6} -alk(en/yn)yl, hydroxy,
15 hydroxy- C_{1-6} -alk(en/yn)yl, C_{1-6} -alk(en/yn)oxy- C_{1-6} -alk(en/yn)yl, e.g. one or two selected from hydroxy, hydroxy- C_{1-6} -alkyl, C_{1-6} -alkyloxy- C_{1-6} -alkyl, C_{1-6} -alkyl, in particular one or two selected from hydroxy, methoxy-methyl, methyl. Typically, R^8 is selected from hydrogen; halogen; cyano; C_{1-6} -alkyl; C_{1-6} -alkyloxy; C_{1-6} -alkylsulfanyl; halo- C_{1-6} -alkyl; NR^xR^y wherein R^x and R^y are independently selected
20 from hydrogen, C_{1-6} -alkyl, cyanomethyl; NR^xR^y wherein R^y is selected from hydrogen, or C_{1-6} -alkyl, and R^x is NR^zR^w - C_{1-6} -alk(en/yn)yl wherein R^z and R^w are independently selected from hydrogen, or C_{1-6} -alkyl; 1-morpholinyl, 1-piperidinyl, 1-azepinyl, 1-piperazinyl, 1-homopiperazinyl, 1-imidazolyl, 1-pyrrolidinyl, 1-azetidyl, 1-pyrrolyl or pyrazolyl, optionally substituted with one or two selected from hydroxy,
25 hydroxy- C_{1-6} -alkyl, C_{1-6} -alkyloxy- C_{1-6} -alkyl, C_{1-6} -alkyl, in particular one or two selected from hydroxy, methoxy-methyl, methyl. To further illustrate without limiting the invention an embodiment of R^8 is hydrogen; another embodiment of R^8 is halogen, such as fluoro, or bromo; a further embodiment of R^8 is C_{1-6} -alkyl, such as methyl; a further embodiment of R^8 is halo- C_{1-6} -alkyl, such as CF_3 .
30

In a further embodiment of the compound of formula I R^9 is selected from hydrogen, halogen, C_{1-6} -alk(en/yn)yl, halo- C_{1-6} -alk(en/yn)yl. Typically, R^9 is selected from

hydrogen, halogen, C₁₋₆-alkyl, halo-C₁₋₆-alkyl. To further illustrate without limiting the invention an embodiment of R⁹ is hydrogen.

5 In a further embodiment of the compound of formula I the dotted line ---- indicates a single bond.

In a further embodiment of the compound of formula I the dotted line ---- indicates a double bond.

10 Typically, the compound of formula I has at least one substituent in the phenyl ring(s), selected from any one of R¹-R⁹, which is different from hydrogen, such as 1, 2, 3, or 4 substituents in the phenyl ring(s), selected from any one of R¹-R⁹, which is/are different from hydrogen, and the remaining substituents are hydrogen. Thus, in a further embodiment 1 substituent selected from any one of R¹-R⁹, which is different
15 from hydrogen, is present in either of the two phenyl rings, such as 1 substituent selected from R¹-R⁵, or the substituent is selected from R⁶-R⁹. In a further embodiment 2 substituents selected from R¹-R⁹, which are different from hydrogen, are present in either of the two phenyl rings, such as 1 substituent selected from R¹-R⁵, and the other selected from R⁶-R⁹, or both substituents are selected from R¹-R⁵; in
20 this respect R² and R³ may be taken together to form the heterocycle as defined above. In a further embodiment 3 substituents selected from R¹-R⁹, which are different from hydrogen, are present in either of the two phenyl rings, such as 2 substituents selected from R¹-R⁵, and the last substituent is selected from R⁶-R⁹. To illustrate this further without limiting the invention, some typical embodiments are outlined hereafter.

25

Thus, in a further embodiment of the compound of formula I one substituent is present which is R² as defined above, except hydrogen. In a further embodiment of the compound of formula I one substituent is present which is R³ as defined above, except hydrogen. In a further embodiment of the compound of formula I two substituents are
30 present being R³ and R⁸, wherein R³ and R⁸ are as defined above, except hydrogen. In a further embodiment of the compound of formula I two substituents are present being R³ and R⁶, wherein R³ and R⁶ are as defined above, except hydrogen. In a further embodiment of the compound of formula I two substituents are present being R³ and

R^7 , wherein R^3 and R^7 are as defined above, except hydrogen. In a further embodiment of the compound of formula I two substituents are present being R^1 and R^3 , wherein R^1 and R^3 are as defined above, except hydrogen. In a further embodiment of the compound of formula I two substituents are present being R^2 and R^3 , wherein R^2 and R^3 are as defined above, except hydrogen, in this respect R^2 and R^3 may be taken together to form the heterocycle as defined above. In a further embodiment of the compound of formula I three substituents are present being R^1 , R^3 and R^8 , wherein R^1 , R^3 and R^8 are as defined above, except hydrogen.

In a further embodiment of the compound of formula I said compound is selected from

4-[2-(2,4-Dimethylphenoxy)phenyl]-1,2,3,6-tetrahydropyridine,
4-[2-(4-Chlorophenoxy)phenyl]-1,2,3,6-tetrahydropyridine,
4-[2-(4-Fluoro-2-methylphenoxy)phenyl]-1,2,3,6-tetrahydropyridine,
4-[2-(4-Fluorophenoxy)phenyl]-1,2,3,6-tetrahydropyridine,
4-[2-(4-Methylphenoxy)phenyl]-1,2,3,6-tetrahydropyridine,
4-[2-(4-Methoxyphenoxy)phenyl]-1,2,3,6-tetrahydropyridine,
4-[2-(2,4-Dimethylphenoxy)phenyl]piperidine,
4-[2-(4-Chlorophenoxy)phenyl]piperidine,
4-[2-(4-Fluoro-2-methylphenoxy)phenyl]piperidine,
4-[2-(4-Fluorophenoxy)phenyl]piperidine,
4-[2-(4-Methylphenoxy)phenyl]piperidine, or

a pharmaceutically acceptable salt thereof. Each of these compounds is considered a specific embodiment and may be subject to individual claims.

The present invention also comprises salts of the present compounds, typically, pharmaceutically acceptable salts. Such salts include pharmaceutical acceptable acid addition salts, pharmaceutically acceptable metal salts, ammonium and alkylated ammonium salts. Acid addition salts include salts of inorganic acids as well as organic acids.

Representative examples of suitable inorganic acids include hydrochloric, hydrobromic, hydroiodic, phosphoric, sulfuric, sulfamic, nitric acids and the like.

Representative examples of suitable organic acids include formic, acetic, trichloroacetic, trifluoroacetic, propionic, benzoic, cinnamic, citric, fumaric, glycolic, itaconic, lactic, methanesulfonic, maleic, malic, malonic, mandelic, oxalic, picric, pyruvic, salicylic, succinic, methane sulfonic, ethanesulfonic, tartaric, ascorbic,
5 pamoic, bismethylene salicylic, ethanedisulfonic, gluconic, citraconic, aspartic, stearic, palmitic, EDTA, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, p-toluenesulfonic acids, theophylline acetic acids, as well as the 8-halothephyllines, for example 8-bromothephylline and the like.

10 Examples of metal salts include lithium, sodium, potassium, magnesium salts and the like.

Examples of ammonium and alkylated ammonium salts include ammonium, methyl-, dimethyl-, trimethyl-, ethyl-, hydroxyethyl-, diethyl-, n-butyl-, sec-butyl-, tert-butyl-,
15 tetramethylammonium salts and the like.

Also intended as pharmaceutical acceptable acid addition salts are the hydrates, which the present compounds, are able to form.

20 Further, the compounds of this invention may exist in unsolvated as well as in solvated forms with pharmaceutically acceptable solvents such as water, ethanol and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of this invention.

25 The compounds of the present invention may have one or more asymmetric centres and it is intended that any optical isomers (i.e. enantiomers or diastereomers), as separated, pure or partially purified optical isomers and any mixtures thereof including racemic mixtures are included within the scope of the invention.

30 Racemic forms can be resolved into the optical antipodes by known methods, for example, by separation of diastereomeric salts thereof with an optically active acid, and liberating the optically active amine compound by treatment with a base. Another method for resolving racemates into the optical antipodes is based upon

chromatography on an optically active matrix. Racemic compounds of the present invention can also be resolved into their optical antipodes, e.g. by fractional crystallization of d- or l- (tartrates, mandelates or camphorsulphonate) salts. The compounds of the present invention may also be resolved by the formation of diastereomeric derivatives.

Additional methods for the resolution of optical isomers, known to those skilled in the art, may be used. Such methods include those discussed by J. Jaques, A. Collet and S. Wilen in "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, New York (1981).

Optically active compounds can also be prepared from optically active starting materials, or by stereoselective synthesis.

Furthermore, when a double bond or a fully or partially saturated ring system is present in the molecule geometric isomers may be formed. It is intended that any geometric isomers, as separated, pure or partially purified geometric isomers or mixtures thereof are included within the scope of the invention. Likewise, molecules having a bond with restricted rotation may form geometric isomers. These are also intended to be included within the scope of the present invention.

Furthermore, some of the compounds of the present invention may exist in different tautomeric forms and it is intended that any tautomeric forms that the compounds are able to form are included within the scope of the present invention.

The invention also encompasses prodrugs of the present compounds, which on administration undergo chemical conversion by metabolic processes before becoming pharmacologically active substances. In general, such prodrugs will be functional derivatives of the compounds of the general formula (I), which are readily convertible in vivo into the required compound of the formula (I). Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

The invention also encompasses active metabolites of the present compounds.

As mentioned above, the compounds of formula I are serotonin reuptake inhibitors,
5 and accordingly may be applicable for the treatment, including prevention, of
affective disorders, such as depression, anxiety disorders including general anxiety
disorder and panic disorder and obsessive compulsive disorder.

Accordingly, in a further aspect the invention relates to a compound of formula I for
10 use as a medicament.

The present invention also relates to a pharmaceutical composition comprising a
compound of formula I and a pharmaceutically acceptable carrier or diluent. The
composition may comprise any one of the embodiments of formula I described above.
15

In an embodiment of the pharmaceutical composition, the compound of formula I is
present in an amount of from about 0.001 to about 100 mg/kg body weight per day.

The present invention also relates to use of a compound of formula I for the
20 preparation of a medicament for the treatment of a disease or disorder, wherein a
serotonin reuptake inhibitor is beneficial. The medicament may comprise any one of
the embodiments of formula I described above.

In particular the present invention also relates to use of a compound of formula I for
25 the preparation of a medicament for the treatment of affective disorders.

In a further embodiment the present invention also relates to use of a compound of
formula I for the preparation of a medicament for the treatment of depression.

30 In a further embodiment the present invention also relates to use of a compound of
formula I for the preparation of a medicament for the treatment of anxiety disorders.

In a further embodiment the present invention also relates to use of a compound of formula I for the preparation of a medicament for the treatment of general anxiety disorder.

- 5 In a further embodiment the present invention also relates to use of a compound of formula I for the preparation of a medicament for the treatment of social anxiety disorder.

- 10 In a further embodiment the present invention also relates to use of a compound of formula I for the preparation of a medicament for the treatment of post traumatic stress disorder.

- 15 In a further embodiment the present invention also relates to use of a compound of formula I for the preparation of a medicament for the treatment of obsessive compulsive disorder.

In a further embodiment the present invention also relates to use of a compound of formula I for the preparation of a medicament for the treatment of panic disorder.

- 20 In a further embodiment the present invention also relates to use of a compound of formula I for the preparation of a medicament for the treatment of panic attacks.

- 25 In a further embodiment the present invention also relates to use of a compound of formula I for the preparation of a medicament for the treatment of specific phobias.

In a further embodiment the present invention also relates to use of a compound of formula I for the preparation of a medicament for the treatment of social phobia.

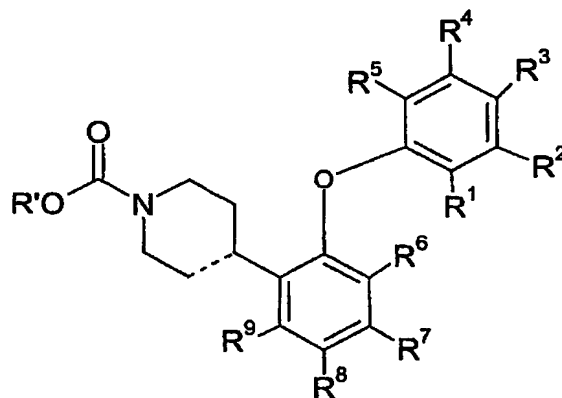
- 30 In a further embodiment the present invention also relates to use of a compound of formula I for the preparation of a medicament for the treatment of agoraphobia.

A further aspect of the invention relates to a method for the treatment of a disease or disorder selected from the group consisting of an affective disorder, such as

- depression, anxiety disorders including general anxiety disorder, social anxiety disorder, post traumatic stress disorder, obsessive compulsive disorder, panic disorder, panic attacks, specific phobias, social phobia and agoraphobia in a living animal body, including a human, comprising administering to a subject in need thereof a
- 5 therapeutically effective amount of a compound of formula I.

In a further aspect the present invention relates to a method of preparing a compound of formula I, comprising

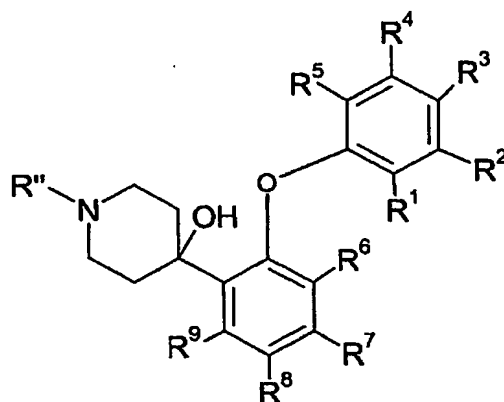
- 10 a) Deprotection or cleavage from a polymer support of a compound with formula II



II

- wherein the dotted line, R^1 - R^9 are as previously described, and R' is a *tert*-butyl, methyl, ethyl, allyl or benzyl group or $R'OCO$ is a solid supported carbamate group;
- 15 or

- b) Dehydrating and optionally simultaneously deprotecting a compound of formula III

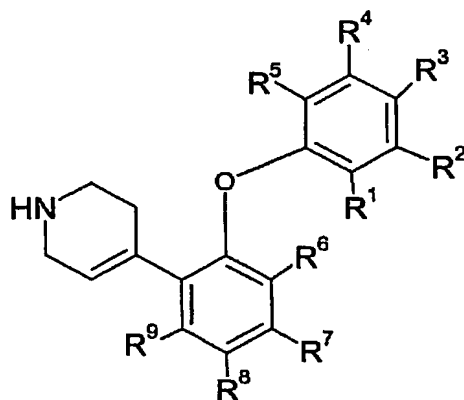


III

wherein R^1 - R^9 are as previously described, and R'' is either a hydrogen atom or a carbamate group $R'OCO$ wherein R' is a *tert*-butyl, methyl, ethyl, allyl or benzyl group or $R'OCO$ is a solid supported carbamate group; or

5

c) Reduction of the double bond in a compound of formula IV



IV

wherein R^1 - R^9 are as previously described.

10

Pharmaceutical compositions

The compounds of the invention may be administered alone or in combination with pharmaceutically acceptable carriers or excipients, in either single or multiple doses.

15 The pharmaceutical compositions according to the invention may be formulated with pharmaceutically acceptable carriers or diluents as well as any other known adjuvants

and excipients in accordance with conventional techniques such as those disclosed in Remington: The Science and Practice of Pharmacy, 19 Edition, Gennaro, Ed., Mack Publishing Co., Easton, PA, 1995.

- 5 The pharmaceutical compositions may be specifically formulated for administration by any suitable route such as the oral, rectal, nasal, pulmonary, topical (including buccal and sublingual), transdermal, intracisternal, intraperitoneal, vaginal and parenteral (including subcutaneous, intramuscular, intrathecal, intravenous and intradermal) route, the oral route being preferred. It will be appreciated that the
10 preferred route will depend on the general condition and age of the subject to be treated, the nature of the condition to be treated and the active ingredient chosen.

Pharmaceutical compositions for oral administration include solid dosage forms such as capsules, tablets, dragees, pills, lozenges, powders and granules. Where
15 appropriate, they can be prepared with coatings such as enteric coatings or they can be formulated so as to provide controlled release of the active ingredient such as sustained or prolonged release according to methods well known in the art.

Liquid dosage forms for oral administration include solutions, emulsions,
20 suspensions, syrups and elixirs.

Pharmaceutical compositions for parenteral administration include sterile aqueous and nonaqueous injectable solutions, dispersions, suspensions or emulsions as well as sterile powders to be reconstituted in sterile injectable solutions or dispersions prior to
25 use. Depot injectable formulations are also contemplated as being within the scope of the present invention.

Other suitable administration forms include suppositories, sprays, ointments, cremes, gels, inhalants, dermal patches, implants etc.

30

A typical oral dosage is in the range of from about 0.001 to about 100 mg/kg body weight per day, preferably from about 0.01 to about 50 mg/kg body weight per day, and more preferred from about 0.05 to about 10 mg/kg body weight per day

administered in one or more dosages such as 1 to 3 dosages. The exact dosage will depend upon the frequency and mode of administration, the sex, age, weight and general condition of the subject treated, the nature and severity of the condition treated and any concomitant diseases to be treated and other factors evident to those skilled in the art.

The formulations may conveniently be presented in unit dosage form by methods known to those skilled in the art. A typical unit dosage form for oral administration one or more times per day such as 1 to 3 times per day may contain from 0.01 to about 1000 mg, preferably from about 0.05 to about 500 mg, and more preferred from about 0.5 mg to about 200 mg.

For parenteral routes such as intravenous, intrathecal, intramuscular and similar administration, typically doses are in the order of about half the dose employed for oral administration.

The compounds of this invention are generally utilized as the free substance or as a pharmaceutically acceptable salt thereof. One example is an acid addition salt of a compound having the utility of a free base. When a compound of the formula (I) contains a free base such salts are prepared in a conventional manner by treating a solution or suspension of a free base of the formula (I) with a chemical equivalent of a pharmaceutically acceptable acid. Representative examples are mentioned above.

For parenteral administration, solutions of the novel compounds of the formula (I) in sterile aqueous solution, aqueous propylene glycol, aqueous vitamin E or sesame or peanut oil may be employed. Such aqueous solutions should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. The aqueous solutions are particularly suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. The sterile aqueous media employed are all readily available by standard techniques known to those skilled in the art.

Suitable pharmaceutical carriers include inert solid diluents or fillers, sterile aqueous

solution and various organic solvents. Examples of solid carriers are lactose, terra alba, sucrose, cyclodextrin, talc, gelatine, agar, pectin, acacia, magnesium stearate, stearic acid and lower alkyl ethers of cellulose. Examples of liquid carriers are syrup, peanut oil, olive oil, phospho lipids, fatty acids, fatty acid amines, polyoxyethylene and water. Similarly, the carrier or diluent may include any sustained release material known in the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax. The pharmaceutical compositions formed by combining the novel compounds of the formula (I) and the pharmaceutical acceptable carriers are then readily administered in a variety of dosage forms suitable for the disclosed routes of administration. The formulations may conveniently be presented in unit dosage form by methods known in the art of pharmacy.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules or tablets, each containing a predetermined amount of the active ingredient, and which may include a suitable excipient. Furthermore, the orally available formulations may be in the form of a powder or granules, a solution or suspension in an aqueous or non-aqueous liquid, or an oil-in-water or water-in-oil liquid emulsion.

If a solid carrier is used for oral administration, the preparation may be a tablet, placed in a hard gelatine capsule in powder or pellet form or it can be in the form of a troche or lozenge.

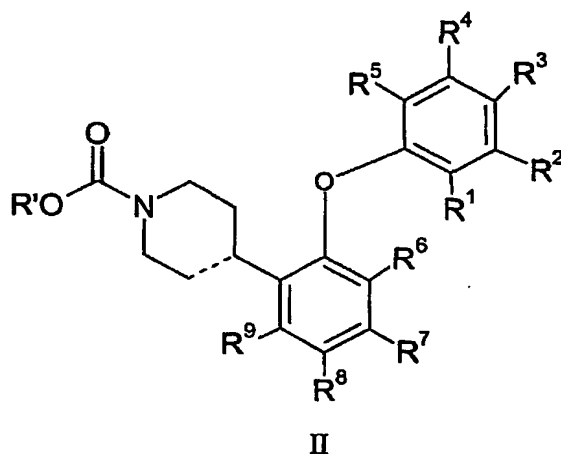
The amount of solid carrier will vary widely but will usually be from about 25 mg to about 1 g.

If a liquid carrier is used, the preparation may be in the form of a syrup, emulsion, soft gelatine capsule or sterile injectable liquid such as an aqueous or non-aqueous liquid suspension or solution.

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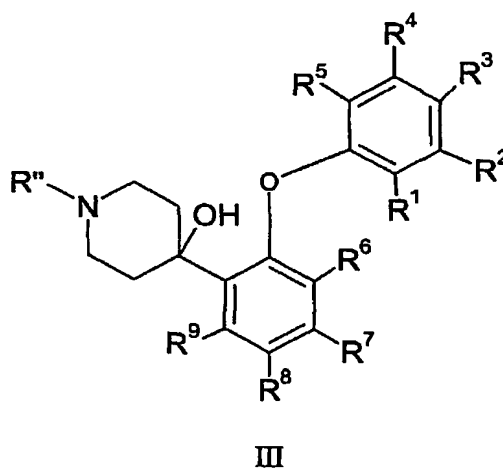
The compounds of the invention are prepared by the following general methods:

a) Deprotection or cleavage from a polymer support of a compound with formula II



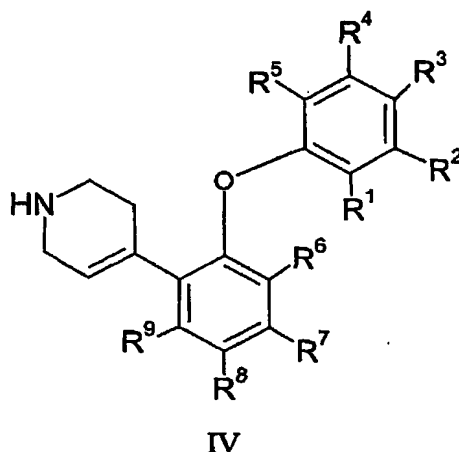
wherein R^1 - R^9 are as previously described, and R' is a *tert*-butyl, methyl, ethyl, allyl or benzyl group or $R'OCO$ is a solid supported carbamate group, such as the Wang resin-based carbamate linker;

b) Dehydrating and optionally simultaneously deprotecting a compound of formula III



wherein R^1 - R^9 are as previously described, and R'' is either a hydrogen atom or a carbamate group $R'OCO$ wherein R' is a *tert*-butyl, methyl, ethyl, allyl or benzyl group or $R'OCO$ is a solid supported carbamate group, such as the Wang resin-based carbamate linker;

c) Reduction of the double bond in a compound of formula IV



IV

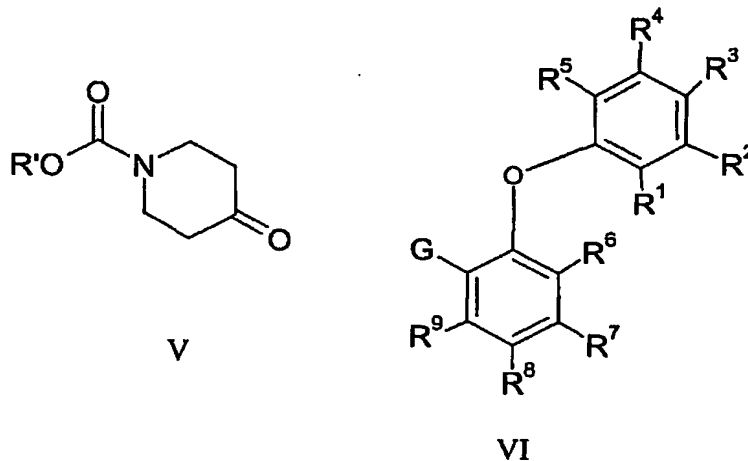
wherein R¹-R⁹ are as previously described.

- 5 The deprotection according to method a) was performed by standard techniques, knowledgeable to those skilled in the art and detailed in the textbook *Protective Groups in Organic Synthesis* T.W.Greene and P.G.M. Wuts, Wiley Interscience, (1991) ISBN 0471623016. The cleavage from a polymer support, such as from the Wang resin-based carbamate linker, according to method a) may be performed
- 10 according to literature known procedures (Zaragoza *Tetrahedron Lett.* 1995, 36, 8677-8678 and Conti et al. *Tetrahedron Lett.* 1997, 38, 2915-2918).

- Starting materials of formula II can be prepared by removal of the hydroxy group of compounds of formula III by a number of methods known to the chemist skilled in the art, e.g. by the use of triethylsilane in trifluoro acidic acid and boron trifluoride diethyl etherate (see *Encyclopaedia of Reagents for Organic Synthesis*, vol 7, Paquette, ed.; John Wiley & Sons, Chichester, 1995, 5122-5123). Starting materials of formula II, which are piperidines, may be prepared by reduction of the double bond of the corresponding tetrahydropyridines by standard hydrogenation procedures, such as e.g.
- 20 catalytic hydrogenation at low pressure (< 3 atm.) in a Parr apparatus.

The dehydration reaction and optional simultaneous deprotection of a compound of formula III according to method b) was performed in a similar manner as described in Palmer et al *J. Med. Chem.* 1997, 40, 1982-1989.

Starting materials of formula III were prepared from the corresponding properly substituted 1-bromo-2-phenoxybenzenes of formula VI (wherein R^1 - R^9 are as previously described, and G is a bromine or iodine atom) by metal-halogen exchange followed by addition of an appropriate electrophile of the formula V (wherein R' is as previously described) in a similar manner as described in Palmer et al. *J. Med. Chem.* 1997, 40, 1982-1989.



The properly substituted 1-bromo-2-phenoxybenzenes were prepared by reaction of properly substituted phenols (the sodium salt of the phenols were prepared in situ by the use of sodium hydride) with properly substituted 1-bromo-2-fluorobenzenes in dimethyl formamide (DMF) at elevated temperature. The diaryl ethers may also be prepared by various modifications of this method (see e.g. Schmittlinger et al *J.Org.Chem.* 1993, 58, 3229-3230; Beugelmans et al *Tetrahedron Lett.* 1994, 35, 5649-5652; Sawyer et al *J.Org.Chem.* 1998, 63, 6338-6343), under Ullmann conditions or via arylation of phenols with arylboronic acids (Evans et al *Tetrahedron Lett* 1998, 39, 2937-2940). Phenols and 1-bromo-2-fluorobenzenes are commercially available.

The reduction of the double bond according to method c) is generally performed by catalytic hydrogenation at low pressure (< 3 atm.) in a Parr apparatus. Starting materials of formula IV may be prepared from compounds of formula II by deprotection as described above.

Examples

- Analytical LC-MS data were obtained on a PE Sciex API 150EX instrument equipped with IonSpray source and Shimadzu LC-8A/SLC-10A LC system. Column: 30 X 4.6 mm Waters Symmetry C18 column with 3.5 μ m particle size; Solvent system: A = water/trifluoroacetic acid (100:0.05) and B = water/acetonitrile/trifluoroacetic acid (5:95:0.03); Method: Linear gradient elution with 90% A to 100% B in 4 min and with a flow rate of 2 mL/min. Purity was determined by integration of the UV (254 nm) and ELSD trace. The retention times (RT) are expressed in minutes.
- Preparative LC-MS-purification was performed on the same instrument. Column: 50 X 20 mm YMC ODS-A with 5 μ m particle size; Method: Linear gradient elution with 80% A to 100% B in 7 min and with a flow rate of 22.7 mL/min. Fraction collection was performed by split-flow MS detection.

Preparation of intermediates

Preparation of substituted 2-bromo-(substituted-phenoxy)benzenes

2-Bromo-(2,4-dimethylphenoxy)benzene

- A solution 2,4-dimethylphenol (2.4 g) in dry dimethyl formamide (DMF) (10 mL) was added drop wise to a mixture of sodium hydride (1.0 g, 60% in mineral oil) and dry DMF (25 mL), and the resulting mixture was stirred at 100 °C for 30 min. To this mixture was further added 1-bromo-2-fluorobenzene (3.5 g) in dry DMF (5 mL), and the resulting mixture was stirred at 150 °C for 6 hours. The mixture was subsequently poured onto an ice/water mixture, and the aqueous phase was extracted with diethyl ether. The combined organic phase was washed with 2N sodium hydroxide, dried (MgSO₄), filtered and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (eluent: heptane) to give the crude product (1.2 g, 70% pure). The crude product was used in the next step without further purification.

The following compounds were prepared in a similar manner:

2-Bromo-(4-chlorophenoxy)benzene

2-Bromo-(4-fluoro-2-methylphenoxy)benzene

2-Bromo-(4-fluorophenoxy)benzene

2-Bromo-(4-methylphenoxy)benzene

2-Bromo-(4-methoxyphenoxy)benzene

5

Preparation of alkyl 4-[2-(substituted-phenoxy)-substituted-phenyl]-4-hydroxypiperidine-1-carboxylates

10

tert-Butyl 4-[2-(2,4-Dimethylphenoxy)phenyl]-4-hydroxy-piperidine-1-carboxylate

15

20

A solution of 2-bromo-(2,4-dimethylphenoxy)benzene (0.7 g) in dry tetrahydrofuran (THF) (3 mL) was added to a solution of nBuLi (1.6 M in hexane, 2 mL) in dry THF (15 mL) at -78 °C. The resulting mixture was stirred at -78 °C for 1 hour and subsequently added a solution of *tert*-butyl 4-oxo-piperidine-1-carboxylate (1.0 g) in dry THF (3 mL). The mixture was stirred for 16 hour at room temperature, and then poured onto a saturated solution of ammonium chloride. The aqueous phase was extracted with diethyl ether, and the combined organic phase was washed with water and brine, and subsequently dried (MgSO₄), filtered and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (eluent: heptane/ethyl acetate 4:1) to give the crude product (0.55 g). The crude product was used in the next step without further purification.

The following compounds were prepared in a similar manner:

25

Ethyl 4-[2-(2,4-Dimethylphenoxy)phenyl]-4-hydroxy-piperidine-1-carboxylate

Ethyl 4-[2-(4-Chlorophenoxy)phenyl]-4-hydroxy-piperidine-1-carboxylate

tert-Butyl 4-[2-(4-Fluoro-2-methylphenoxy)phenyl]-4-hydroxy-piperidine-1-carboxylate

Ethyl 4-[2-(4-Fluoro-2-methylphenoxy)phenyl]-4-hydroxy-piperidine-1-carboxylate

30

Ethyl 4-[2-(4-Fluorophenoxy)phenyl]-4-hydroxy-piperidine-1-carboxylate

tert-Butyl 4-[2-(4-Methylphenoxy)phenyl]-4-hydroxy-piperidine-1-carboxylate

Ethyl 4-[2-(4-Methylphenoxy)phenyl]-4-hydroxy-piperidine-1-carboxylate

tert-Butyl 4-[2-(4-Methoxyphenoxy)phenyl]-4-hydroxy-piperidine-1-carboxylate

Compounds of the invention:**Preparation of 4-[2-(substituted-phenoxy)-substituted-phenyl]-1,2,3,6-tetrahydropyridines****1a, 4-[2-(2,4-Dimethylphenoxy)phenyl]-1,2,3,6-tetrahydropyridine**

A mixture of *tert*-butyl 4-[2-(2,4-dimethylphenoxy)phenyl]-4-hydroxy-piperidine-1-carboxylate (0.5 g) and a mixture of acidic acid and conc. hydrochloride acid (3:1) was boiled under reflux for 16 hours. The mixture was cooled, poured into alkaline water and extracted with ethyl acetate. The combined organic phase was dried (MgSO₄), filtered and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (eluent: ethyl acetate/methanol/triethylamine 8:2:1) to give the target compound (11 mg, 3%). LC/MS (m/z) 280 (MH⁺); RT = 2.16; purity (UV, ELSD): 85%, 97%.

The following compounds were prepared in a similar manner:

1b, 4-[2-(4-Chlorophenoxy)phenyl]-1,2,3,6-tetrahydropyridine

From ethyl 4-[2-(4-chlorophenoxy)phenyl]-4-hydroxy-piperidine-1-carboxylate. LC/MS (m/z) 286 (MH⁺); RT = 2.10; purity (UV, ELSD): 85%, 95%; yield: 33 mg (6%).

1c, 4-[2-(4-Fluoro-2-methylphenoxy)phenyl]-1,2,3,6-tetrahydropyridine

From *tert*-butyl 4-[2-(4-fluoro-2-methylphenoxy)phenyl]-4-hydroxy-piperidine-1-carboxylate. LC/MS (m/z) 284 (MH⁺); RT = 2.08; purity (UV, ELSD): 97%, 99%; yield: 100 mg (21%).

1d, 4-[2-(4-Fluorophenoxy)phenyl]-1,2,3,6-tetrahydropyridine

From ethyl 4-[2-(4-fluorophenoxy)phenyl]-4-hydroxy-piperidine-1-carboxylate. LC/MS (m/z) 270 (MH⁺); RT = 1.93; purity (UV, ELSD): 87%, 97%; yield: 45 mg (11%).

1e, 4-[2-(4-Methylphenoxy)phenyl]-1,2,3,6-tetrahydropyridine

From *tert*-butyl 4-[2-(4-methylphenoxy)phenyl]-4-hydroxy-piperidine-1-carboxylate. LC/MS (*m/z*) 266 (MH^+); RT = 2.04; purity (UV, ELSD): 98%, 99%; yield: 250 mg (24%).

5 **1f, 4-[2-(4-Methoxyphenoxy)phenyl]-1,2,3,6-tetrahydropyridine**

From *tert*-butyl 4-[2-(4-methoxyphenoxy)phenyl]-4-hydroxy-piperidine-1-carboxylate. LC/MS (*m/z*) 282 (MH^+); RT = 1.95; purity (UV, ELSD): 79%, 99%; yield: 14.7 mg (19%).

10 **Preparation of 4-[2-(substituted-phenoxy)-substituted-phenyl]piperidines**

2a, 4-[2-(2,4-Dimethylphenoxy)phenyl]piperidine

A mixture of ethyl 4-[2-(2,4-dimethylphenoxy)phenyl]-4-hydroxy-piperidine-1-carboxylate (0.6 g), dichloromethane (25 mL), triethylsilane (1 mL), trifluoro acidic acid (0.1 mL) and boron trifluoride diethyl etherate (0.2 mL) was stirred at room
15 temperature for 16 hours. The resulting mixture was poured onto alkaline water and subsequently extracted with ethyl acetate. The combined organic phase was dried ($MgSO_4$), filtered and concentrated in vacuo (0.4 g). The residue was dissolved in a mixture of conc. hydrochloric acid and acidic acid (1:3) (25 mL) and boiled under
20 reflux for 16 hours. The mixture was poured onto alkaline water and subsequently extracted with ethyl acetate. The combined organic phase was dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (eluent: ethyl acetate/methanol/triethylamine 8:2:2) to give the target
25 compound (10.6 mg, 3%). LC/MS (*m/z*) 282 (MH^+); RT = 2.22; purity (UV, ELSD): 67%, 83%.

The following compounds were prepared in a similar manner:

2b, 4-[2-(4-Chlorophenoxy)phenyl]piperidine

From ethyl 4-[2-(4-chlorophenoxy)phenyl]-4-hydroxy-piperidine-1-carboxylate.
30 LC/MS (*m/z*) 288 (MH^+); RT = 2.1; purity (UV, ELSD): 96%, 97%; yield: 41 mg (7%).

2c, 4-[2-(4-Fluoro-2-methylphenoxy)phenyl]piperidine

From ethyl 4-[2-(4-fluoro-2-methylphenoxy)phenyl]-4-hydroxy-piperidine-1-carboxylate. LC/MS (m/z) 286 (MH^+); RT = 2.1; purity (UV, ELSD): 89%, 99%; yield: 51 mg (8%).

5 **2d, 4-[2-(4-Fluorophenoxy)phenyl]piperidine**

From ethyl 4-[2-(4-fluorophenoxy)phenyl]-4-hydroxy-piperidine-1-carboxylate. LC/MS (m/z) 272 (MH^+); RT = 1.97; purity (UV, ELSD): 91%, 99%; yield: 7 mg (5%).

10 **2e, 4-[2-(4-Methylphenoxy)phenyl]piperidine**

From ethyl 4-[2-(4-methylphenoxy)phenyl]-4-hydroxy-piperidine-1-carboxylate. LC/MS (m/z) 268 (MH^+); RT = 2.12; purity (UV, ELSD): 88%, 93%; yield: 8 mg (1%).

15 **Measurements of [3H]-5-HT uptake into rat cortical synaptosomes.**

Whole brains from male Wistar rats (125-225 g), excluding cerebellum, are homogenized in 0.32 M sucrose supplemented with 1mM nialamid with a glass/teflon homogenizer. The homogenate is centrifuged at 600 x g for 10 min at 4 °C. The pellet is discarded and the supernatant is centrifuged at 20.000 x g for 55 min. The final pellet is
20 homogenized (20 sec) in this assay buffer (0.5 mg original tissue/well). Test compounds (or buffer) and 10 nM [3H]-5-HT are added to 96 well plates and shaken briefly. Composition of assay buffer: 123 mM NaCl, 4.82 mM KCl, 0.973 mM $CaCl_2$, 1.12 mM $MgSO_4$, 12.66 mM Na_2HPO_4 , 2.97 mM NaH_2PO_4 , 0.162 mM EDTA, 10 mM glucose and 1 mM ascorbic acid. Buffer is oxygenated with 95% O_2 /5% CO_2 for 10 min at 37 °C
25 and pH is adjusted 7.4. The incubation is started by adding tissue to a final assay volume of 0.2 mL. After 15 min incubation with radioligand at 37 °C, samples are filtered directly on Unifilter GF/C glass fiber filters (soaked for 1 hour in 0.1% polyethylenimine) under vacuum and immediately washed with 3 x 0.2 ml assay buffer. Non-specific uptake is determined using citalopram (10 μ M final concentration).
30 Citalopram is included as reference in all experiments as dose-response curve.

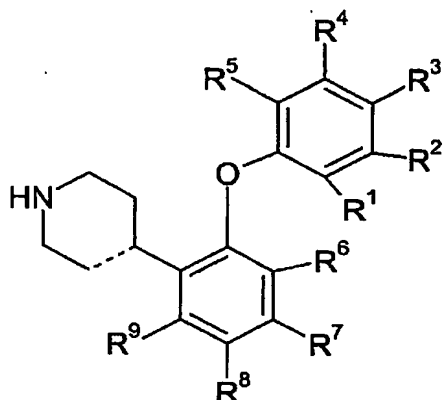
Measurements of [3H]noradrenaline uptake into rat cortical synaptosomes.

Fresh cortex from male Wistar rats (125-225 g) are homogenized in 0.4M sucrose with a glass/teflon homogenizer. The homogenate is centrifuged at 600 x g for 10 min at 4 °C. The pellet is discarded and the supernatant is centrifuged at 20.000 x g for 55 min. The final pellet is homogenized (20 sec) in this assay buffer (6 mg original
5 tissue/mL = 4 mg/well). Test compounds (or buffer) and 10 nM [³H]-noradrenaline are added to deep 96 well plates and shaken briefly. Composition of assay buffer: 123 mM NaCl, 4.82 mM KCl, 0.973 mM CaCl₂, 1.12 mM MgSO₄, 12.66 mM Na₂HPO₄, 2.97 mM NaH₂PO₄, 0.162 mM EDTA, 10 mM glucose and 1 mM ascorbic acid. Buffer is oxygenated with 95% O₂/5% CO₂ for 10 min at 37 °C and pH is adjusted 7.4.
10 The incubation is started by adding tissue to a final assay volume of 1 ml. After 15 min incubation with radioligand at 37 °C, samples are filtered directly on Unifilter GF/C glass fiber filters (soaked for 1 hour in 0.1% polyethylenimine) under vacuum and immediately washed with 3 x 1 mL assay buffer. Non-specific uptake is determined using talsupram (10 µM final concentration). Duloxetine is included as
15 reference in all experiments as dose-response curve.

Results of the experiments showed that the tested compounds of the invention inhibit the norepinephrine and serotonin reuptake with IC₅₀ below 200 nM.

Claims:

1. A compound represented by the general formula I



5

Wherein

the dotted line ---- indicates a single bond or a double bond;

- R^1, R^2, R^3, R^4, R^5 are independently selected from hydrogen, halogen, cyano, C_{1-6} -alk(en/yn)yl, C_{1-6} -alk(en/yn)yoxy, C_{1-6} -alk(en/yn)ylsulfanyl, hydroxy, hydroxy- C_{1-6} -alk(en/yn)yl, halo- C_{1-6} -alk(en/yn)yl, halo- C_{1-6} -alk(en/yn)yoxy, or NR^xR^y wherein R^x and R^y are independently selected from hydrogen, C_{1-6} -alk(en/yn)yl, cyano- C_{1-6} -alk(en/yn)yl, C_{3-8} -cycloalk(en)yl, C_{3-8} -cycloalk(en)yl- C_{1-6} -alk(en/yn)yl, or NR^zR^w - C_{1-6} -alk(en/yn)yl, wherein R^z and R^w are independently selected from hydrogen, C_{1-6} -alk(en/yn)yl, C_{3-8} -cycloalk(en)yl, or C_{3-8} -cycloalk(en)yl- C_{1-6} -alk(en/yn)yl; or R^x and R^y together with the nitrogen to which they are attached form a 3-7-membered ring which optionally contains one further heteroatom; or

- R^2 and R^3 together form a heterocycle fused to the phenyl ring selected from
- 20 ; and R^1, R^4, R^5 are as defined above;

R^6, R^7, R^8, R^9 are independently selected from hydrogen, halogen, C_{1-6} -alk(en/yn)yl, C_{1-6} -alk(en/yn)yoxy, C_{1-6} -alk(en/yn)ylsulfanyl, hydroxy, hydroxy- C_{1-6} -alk(en/yn)yl, halo- C_{1-6} -alk(en/yn)yl, halo- C_{1-6} -alk(en/yn)yoxy, or NR^xR^y wherein R^x and R^y are

independently selected from hydrogen, C₁₋₆-alk(en/yn)yl, cyano-C₁₋₆-alk(en/yn)yl, C₃₋₈-cycloalk(en)yl, C₃₋₈-cycloalk(en)yl-C₁₋₆-alk(en/yn)yl, or NR^zR^w-C₁₋₆-alk(en/yn)yl, wherein R^z and R^w are independently selected from hydrogen, C₁₋₆-alk(en/yn)yl, C₃₋₈-cycloalk(en)yl, or C₃₋₈-cycloalk(en)yl-C₁₋₆-alk(en/yn)yl; or R^x and R^y together with the nitrogen to which they are attached form a 3-7-membered ring which optionally contains one further heteroatom;

provided that at least one of R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, and R⁹ is different from hydrogen;

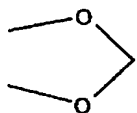
10 or a salt thereof.

2. The compound of claim 1, wherein R¹ is selected from hydrogen, halogen, cyano, C₁₋₆-alk(en/yn)yl, C₁₋₆-alk(en/yn)yl, C₁₋₆-alk(en/yn)ylsulfonyl, halo-C₁₋₆-alk(en/yn)yl, or NR^xR^y wherein R^x and R^y are independently selected from hydrogen, C₁₋₆-alk(en/yn)yl, cyano-C₁₋₆-alk(en/yn)yl, C₃₋₈-cycloalk(en)yl, C₃₋₈-cycloalk(en)yl-C₁₋₆-alk(en/yn)yl, or NR^zR^w-C₁₋₆-alk(en/yn)yl, wherein R^z and R^w are independently selected from hydrogen, C₁₋₆-alk(en/yn)yl, C₃₋₈-cycloalk(en)yl, or C₃₋₈-cycloalk(en)yl-C₁₋₆-alk(en/yn)yl, provided that if one of R^x and R^y is NR^zR^w-C₁₋₆-alk(en/yn)yl then the other is selected from hydrogen, C₁₋₆-alk(en/yn)yl, cyano-C₁₋₆-alk(en/yn)yl, C₃₋₈-cycloalk(en)yl, or C₃₋₈-cycloalk(en)yl-C₁₋₆-alk(en/yn)yl; or R^x and R^y together with the nitrogen to which they are attached form a 3-7-membered ring which optionally contains one further heteroatom.

25 3. The compound of any one of claims 1-2, wherein R² is selected from hydrogen, halogen, cyano, C₁₋₆-alk(en/yn)yl, C₁₋₆-alk(en/yn)yloxy, C₁₋₆-alk(en/yn)ylsulfanyl, halo-C₁₋₆-alk(en/yn)yl.

4. The compound of any one of claims 1-3, wherein R³ is selected from hydrogen, halogen, cyano, C₁₋₆-alk(en/yn)yl, C₁₋₆-alk(en/yn)yloxy, C₁₋₆-alk(en/yn)ylsulfanyl, halo-C₁₋₆-alk(en/yn)yl.

5. The compound of any one of claims 1-2, wherein R² and R³ together form a heterocycle fused to the phenyl ring selected from



6. The compound of any one of claims 1-5 wherein R^4 is selected from hydrogen, halogen, cyano, C_{1-6} -alk(en/yn)yl, C_{1-6} -alk(en/yn)ylloxy, C_{1-6} -alk(en/yn)ylsulfanyl, halo- C_{1-6} -alk(en/yn)yl.
7. The compound of any one of claims 1-6 wherein R^5 is selected from hydrogen, halogen, cyano, C_{1-6} -alk(en/yn)yl, C_{1-6} -alk(en/yn)ylloxy, C_{1-6} -alk(en/yn)ylsulfanyl, halo- C_{1-6} -alk(en/yn)yl, or NR^xR^y wherein R^x and R^y are independently selected from hydrogen, C_{1-6} -alk(en/yn)yl, cyano- C_{1-6} -alk(en/yn)yl, C_{3-8} -cycloalk(en)yl, C_{3-8} -cycloalk(en)yl- C_{1-6} -alk(en/yn)yl, or NR^zR^w - C_{1-6} -alk(en/yn)yl, wherein R^z and R^w are independently selected from hydrogen, C_{1-6} -alk(en/yn)yl, C_{3-8} -cycloalk(en)yl, or C_{3-8} -cycloalk(en)yl- C_{1-6} -alk(en/yn)yl, provided that if one of R^x and R^y is NR^zR^w - C_{1-6} -alk(en/yn)yl then the other is selected from hydrogen, C_{1-6} -alk(en/yn)yl, cyano- C_{1-6} -alk(en/yn)yl, C_{3-8} -cycloalk(en)yl, or C_{3-8} -cycloalk(en)yl- C_{1-6} -alk(en/yn)yl; or R^x and R^y together with the nitrogen to which they are attached form a 3-7-membered ring which optionally contains one further heteroatom.
8. The compound of any one of claims 1-7 wherein R^6 is selected from hydrogen, halogen, C_{1-6} -alk(en/yn)yl, halo- C_{1-6} -alk(en/yn)yl.
9. The compound of any one of claims 1-8 wherein R^7 is selected from hydrogen, halogen, C_{1-6} -alk(en/yn)yl, halo- C_{1-6} -alk(en/yn)yl.
10. The compound of any one of claims 1-9 wherein R^8 is selected from hydrogen, halogen, C_{1-6} -alk(en/yn)yl, halo- C_{1-6} -alk(en/yn)yl, or NR^xR^y wherein R^x and R^y are independently selected from hydrogen, C_{1-6} -alk(en/yn)yl, cyano- C_{1-6} -alk(en/yn)yl, C_{3-8} -cycloalk(en)yl, C_{3-8} -cycloalk(en)yl- C_{1-6} -alk(en/yn)yl, or NR^zR^w - C_{1-6} -alk(en/yn)yl, wherein R^z and R^w are independently selected from hydrogen, C_{1-6} -alk(en/yn)yl, C_{3-8} -cycloalk(en)yl, or C_{3-8} -cycloalk(en)yl- C_{1-6} -alk(en/yn)yl, provided that if one of R^x and R^y is NR^zR^w - C_{1-6} -alk(en/yn)yl then the other is selected from hydrogen, C_{1-6} -

alk(en/yn)yl, cyano-C₁₋₆-alk(en/yn)yl, C₃₋₈-cycloalk(en)yl, or C₃₋₈-cycloalk(en)yl-C₁₋₆-alk(en/yn)yl; or R^x and R^y together with the nitrogen to which they are attached form a 3-7-membered ring which optionally contains one further heteroatom.

5 11. The compound of any one of claims 1-10 wherein R⁹ is selected from hydrogen, halogen, C₁₋₆-alk(en/yn)yl, halo-C₁₋₆-alk(en/yn)yl.

12. The compound of any one of claims 1-11 wherein the dotted line ---- indicates a single bond.

10

13. The compound of any one of claims 1-11 wherein the dotted line ---- indicates a double bond.

14. The compound of claim 1, said compound being

15 4-[2-(2,4-Dimethylphenoxy)phenyl]-1,2,3,6-tetrahydropyridine,
4-[2-(4-Chlorophenoxy)phenyl]-1,2,3,6-tetrahydropyridine,
4-[2-(4-Fluoro-2-methylphenoxy)phenyl]-1,2,3,6-tetrahydropyridine,
4-[2-(4-Fluorophenoxy)phenyl]-1,2,3,6-tetrahydropyridine,
4-[2-(4-Methylphenoxy)phenyl]-1,2,3,6-tetrahydropyridine,
20 4-[2-(4-Methoxyphenoxy)phenyl]-1,2,3,6-tetrahydropyridine,
4-[2-(2,4-Dimethylphenoxy)phenyl]piperidine,
4-[2-(4-Chlorophenoxy)phenyl]piperidine,
4-[2-(4-Fluoro-2-methylphenoxy)phenyl]piperidine,
4-[2-(4-Fluorophenoxy)phenyl]piperidine,
25 4-[2-(4-Methylphenoxy)phenyl]piperidine,
or a pharmaceutically acceptable salt thereof.

15. A pharmaceutical composition comprising a compound of any one of claims 1-14 or a pharmaceutically acceptable acid addition salt thereof and at least one
30 pharmaceutically acceptable carrier or diluent.

16. The use of a compound of any one of claims 1 to 14 or a pharmaceutically acceptable acid addition salt thereof for the preparation of a medicament for the

treatment of affective disorders, such as depression, anxiety disorders including general anxiety disorder, social anxiety disorder, post traumatic stress disorder, obsessive compulsive disorder, panic disorder, panic attacks, specific phobias, social phobia and agoraphobia.

5

17. A method for the treatment of an affective disorder, such as depression, anxiety disorders including general anxiety disorder, social anxiety disorder, post traumatic stress disorder, obsessive compulsive disorder, panic disorder, panic attacks, specific phobias, social phobia and agoraphobia in a living animal body, including a
- 10 human, comprising administering a therapeutically effective amount of a compound of any one of claims 1- 14 or a pharmaceutically acceptable acid addition salt thereof.

18. A compound of any one of claims 1-14 for use as a medicament.

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